REMARKS/ARGUMENTS

Claims 30, 71, 75-76, 85-89, 93 and 95-115, are pending in the present application. Support for the amendments *supra* can be found throughout the specification and claims as filed. For example, the term "soluble tumor-associated antigen" – see for example, page 20, lines 21-25, which states "an additional composition of the present invention may also include a modified antigen, wherein a soluble, preferably multiepitopic, antigen is modified by binding to a binding agent". The term "binding agent" is elsewhere defined in the specification as including antibodies.

Applicant asserts that no new matter has been added by amendment. Issues raised in the Office Action will be addressed in the order they were raised by the Examiner.

35 U.S.C. § 112, SECOND PARAGRAPH

Claim 94 was rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. This rejection is moot in view of the cancellation of that claim.

35 U.S.C. § 112, FIRST PARAGRAPH

Claims 30, 71, 73-76, 85-89, 91-96 and 98-115 were rejected as failing to comply with the written description requirement. In particular, the Examiner has stated that there is insufficient support for the term "soluble complexes". Applicants respectfully disagree. One of ordinary skill in the art would have reasonably understood the description in the application of combining a soluble antigen with a binding agent, particularly an antibody, and its intended use of being administered to a patient as a process producing a soluble complex. Nevertheless, in order to expedite prosecution, Applicants have amended the claims to recite the combination of an antibody and a soluble antigen.

To the extent this rejection is applied to the currently pending claims, Applicants respectfully request reconsideration and withdrawal of the rejection.

ART REJECTIONS

Applicants note with appreciation that claim 89 was found to be patentable over the art.

Claims 30, 71, 75-76, 85-88, 93 and 95-115 were rejected by the Examiner under 35 U.S.C. § 103 as allegedly being obvious in view of the combination of six principle references, namely Kedar et al., Crowley et al., Steinman et al., Sallusto et al., De La Salle et al. and Schwartz et al. In particular, the Examiner alleges that

> One of skill in the art would recognize after reading the above prior art references, that dendritic cells are capable of taking up soluble antigen in the form of antigen-antibody complexes in a process that involves internalization from the Fc receptor which is separate from the process of uptaking particulate antigens, and that antigens which are internalized by dendritic cells are processed into immunogenic fragments which are presented in the surface of said dendritic cell. One of skill in the art would also recognize that if a complex of exogenous antigen were internalized by a dendritic cell more than one immunogenic epitope can be presented to a T-cell, such as illustrated in the teachings of Crowley et al. One of skill in the art would be motivated to provide more than one immunogenic epitope of a tumor associated antigen in order to activate more than one T-cell against said antigen after reading the teachings of Kadar et al. on the desirability of having several T-cell clones and antibodies directed against different antigenic epitopes of the tumor in order to circumvent the problem of antigenic heterogeneity exhibited by a tumor mass.

However, the use of a complex formed from a soluble tumor-associated antigen and an antibody, e.g., administered as a complex, is particularly unique because that complex has properties and advantages not taught in the prior art. As described in the present application, the administration of the claimed antibody/tumor-associated antigen complexes induces a multiepitopic response to one or more other epitopes of the tumor-associated antigen. That response was found to be surprisingly more robust that the administration of the tumor-associated antigen alone. Indeed, in certain instances, the antigen alone is weakly or non-immunogenic – as a self antigen.

In contrast, the art relied on by the Examiner is entirely devoid of any teaching or suggestion of the desirability of such a combination.

1. The Examiner alleges that the Kedar et al. reference teaches the desirability of having several T-cell clones directed against different antigenic epitopes of a tumor. However, that reference does not teach or suggest that antibody/tumor-associated antigen complexes could be used to invoke such as response.

2. The Crowley et al. reference is cited by the Examiner for teaching that dendritic cells exposed *in vivo* to exogenous antigen can present multiple immunogenic epitopes. As above, the Crowley et al. reference entirely fails to suggest the use of antigen/antibody complexes or recognize the advantages of such complexes.

3. In similar fashion, the Examiner relies on Steinman et al. to illustrate the understanding in the art that dendritic cells can process complex antigens into peptides that are presented by self MHC products. As above, the Steinman et al. paper offers no guidance or suggestion to use the claimed complexes derived soluble tumor-associated antigen and antibody.

4. Sallusto et al. is yet another reference relied upon by the Examiner in making the outstanding obviousness rejection, but as above, teaches nothing more than known role of dendritic cells in antigen processing and completely misses the point or advantages of administering the claimed antigen/antibody complexes to better harness those biological events.

5. The De La Salle et al. reference is offered by the Examiner as teaching the role of Langerhan's cells in processing antigen presented in vivo by antigen-antibody complexes. However, this reference in no way teaches or suggests the benefits of using of complexes derived from soluble tumor-associated antigen and antibody. De La Salle et al. fail to recognize that such complexes have the unexpected benefit of being to elicit an effective and multiepitopic response against a self antigen – e.g., the tumor antigen.

6. Finally, the Examiner relies on Schwartz to teach that various tumors, such as breast, ovarian, prostate and gastrointestinal tumors present and shed antigens associated with those tumors. Applicants agree that such antigens and the general process of tumor antigen shedding are well known – and hence support the broadly enabling teachings of the present application. However, Schwartz et al. does not teach that such antigens can or should be administered therapeutically in the form of a complex with antibody.

The remaining references cited by the Examiner, to support rejection of particular dependent claims, fails to bridge the gap between the pending claims and these six references.

Alone or in combination, the art cited by the Examiner plainly fails to make any reasonable suggestion to one skilled in the art that complexes derived from soluble tumor-associated antigen and antibody would have any particular benefit. The prior art neither provides

the requisite motivation to make the claimed combination, nor provide one skilled in the art any reasonable expectation for success in administering such combinations. That teaching is found solely in the present application.

Applicants can only conclude that the current rejection is premised on the impermissible use of hindsight, using the claims as a blueprint to pick and chose from the art. The outstanding Office Action provides to factual basis to support the Examiner's conclusion. Should the Examiner maintain the present rejection, Applicants respectfully request that the factual basis for the combination of references be specifically articulated by the Examiner.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. AREX-P02-004.**

Respectfully Submitted,

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Megan Jamroz, Ph.D.
Registration No.: 54,196

ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant